



PATENT
Docket No.: 19603/4230 (CRF D-2238A)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Goldman et al.)	Examiner:
)	Richard Hutson
Serial No.	:	09/282,239)	
Cnfrm. No.	:	To Be Assigned)	Art Unit:
)	1652
Filed	:	March 31, 1999)	
For	:	A METHOD FOR ISOLATING AND)	
		PURIFYING OLIGODENDROCYTES)	
		AND OLIGODENDROCYTE)	
		PROGENITOR CELLS)	

THIRD DECLARATION OF STEVEN A. GOLDMAN UNDER 37 C.F.R. §1.132

Mail Stop
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, STEVEN A. GOLDMAN, pursuant to 37 C.F.R. § 1.132, declare:

1. I received B.A. degrees in Biology and Psychology from the University of Pennsylvania in 1978, a Ph.D. degree in Neurobiology from Rockefeller University in 1983, and an M.D. degree from Cornell University Medical College in 1984.

2. I am a Professor and Chief of the Division of Cell and Gene Therapy of the Department of Neurology, University of Rochester Medical Center, Rochester, New York, where I am the Glenn-Zutes Chair in Biology of the Aging Brain.

3. I am a named inventor of the above patent application.

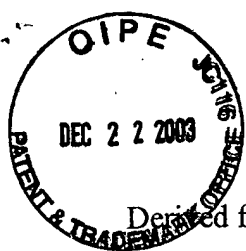
4. I am familiar with U.S. Patent No. 5,726,145 to Bottenstein ("Bottenstein") and U.S. Patent No. 6,361,996 to Rao, et. al., ("Rao").

5. Rao et al. (Rao et al., "Glial-Restricted Precursors are Derived from Multipotential Neuroepithelial Stem Cells," *Dev. Biol.* 188:48-63 (1997), attached hereto as

Exhibit 1) clearly demonstrate the strong astrocytic bias of their cells, which generated few, if any, oligodendrocytes.

6. There are fundamental differences between the lineage restriction and potential of neonatal and adult oligodendrocyte progenitor cells (Noble et al., "The O2A (Adult) Progenitor Cell: A Glial Stem Cell of the Adult Central Nervous System," *Seminars in Cell Biol.* 3:413-22 (1992), attached hereto as Exhibit 2; and Windrem et al., "Fetal and Adult Human Oligodendrocyte Progenitor Cells Effectively Myelinate Dysmyelinated Brain," *Nature Medicine* (January, 2004) (in press), attached hereto as Exhibit 3, which has been accepted for publication (see attached Exhibit 4)). These biological differences between perinatal and adult progenitor cells were not recognized by Rao or Bottenstein, whose cells were restricted to neonatal rodent derivation.

7. Rat oligodendrocyte progenitors are neither biologically nor phenotypically homologous to human oligodendrocyte progenitor cells. Specifically, rat oligodendrocyte progenitors and oligodendrocytes both express the antigenic marker recognized by monoclonal antibody O4. In contrast, this marker is expressed by human oligodendrocytes and their immature forms, but NOT by mitotic oligodendrocyte progenitor cells (See Armstrong et al., "Pre-Oligodendrocytes from Adult Human CNS," *J. Neurosci.* 12: 1538-47, 1992; Gogate et al., "Plasticity in the Adult Human Oligodendrocyte Lineage," *J. Neurosci.* 14:4571-87 (1994), attached hereto as Exhibit 5; Kirschenbaum et al., "In vitro Neuronal Production and Differentiation by Precursor Cells Derived from the Adult Human Forebrain," *Cerebral Cortex* 6: 576-89 (1994); Roy et al., "Identification, Isolation, and Promoter-Defined Separation of Mitotic Oligodendrocyte Progenitor Cells From the Adult Human Subcortical White Matter," *J. Neurosci.* 19: 9986-95 (1999) ("Roy, 1999"), attached hereto as Exhibit 6). As a result, human oligodendrocyte progenitor cells cannot be acquired through the use of O4 as a selection marker, and O4-defined human oligodendroglial cells cannot act as mitotically-competent progenitor cells. This is in sharp distinction to the rat brain, in which the use of this marker can identify oligodendrocyte progenitors. Neither Rao nor Bottenstein recognized the non-applicability of this marker to the separation of human oligodendrocyte progenitor cells. In humans, mitotic cells biased strongly towards the oligodendrocyte lineage are instead recognized by the antigenic phenotype O4⁺/PSA-NCAM⁺/A2B5⁺, which comprise a distinct subpopulation in which the CNP2 promoter is transcriptionally activated (Roy, 1999; Windrem et al., "Progenitor Cells



Derived from the Adult Human Subcortical White Matter Disperse and Differentiate as Oligodendrocytes Within Demyelinated Regions of the Rat Brain," *J. Neurosci. Res.* 69:966-75 (2002), attached hereto as Exhibit 7; Nunes et al., "Identification and Isolation of Multipotential Neural Progenitor Cells from the Subcortical White Matter of the Adult Human Brain," *Nature Med.* 9: 439-47 (2003); attached hereto as Exhibit 8).

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 12-17-03



Steven A. Goldman, M.D., Ph.D.

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